Subject: INFLUENCE OF RENAL VASODILATING INFUSIONS OF FENOLDOPAM (SK&F 82526) ON THE HEMODYNAMIC RESPONSE OF INHALATION ANESTHETICS IN THE RAT

Authors: W.F. Ebling, Ph.D., M. Nunez, BSc., J. Field, ASc.

Affiliation: Department of Anesthesia, Stanford University, Stanford, CA 94305 and Veterans Administration Medical Center, Palo Alto, CA 94304

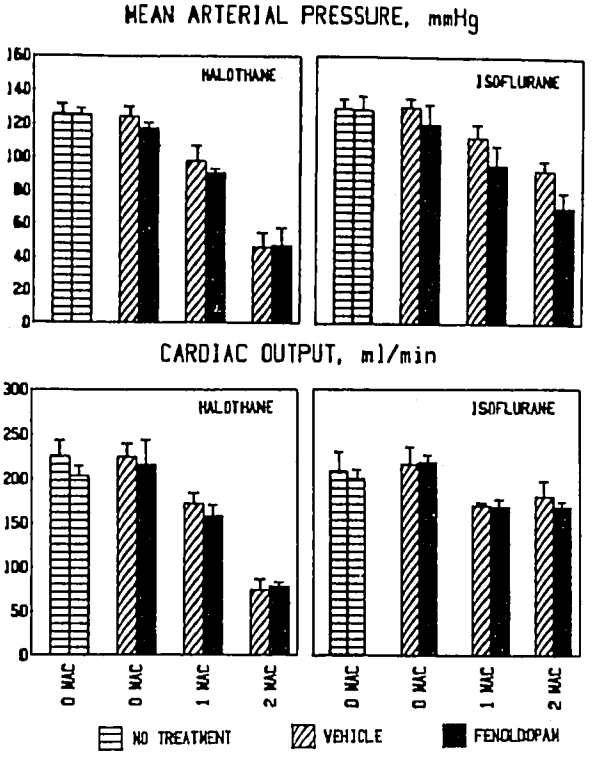
Introduction: Isoflurane and halothane produce profound hypotension and diminish renal blood flow which when added to the insult of surgery may be detrimental to the kidney. Depressed renal function is observed for several hours to several days following anesthesia especially if extended intraoperative hypotension occurs[1]. Cardiac and aortic surgical patients are particularly subject to increased risk of postoperative renal disfunction[2]. Fenoldopam(F), a new potent and selective dopamine DA1 agonist, may prove to limit renal sequela following anesthesia. It has been shown to be a potent renal vasodilator and diuretic at doses as low as 0.1 to 1 ug/min/kg[3]. F does not stimulate sympathetic alpha or beta receptors and thus does not share the "renal window" effect which limits the beneficial effects of dopamine. However, at doses greater then 2.5 ug/min/kg F produces hypotensive effects which could dangerously interact with anesthetics. Therefore, the hemodynamic response of inhalation anesthetics in the presence of maximally vasodilating infusions of F was assessed in an animal model to examine the potential intraoperative safety of this new selective renal vasodilator.

Methods: Male Sprague Dawley rats (350-375 gm) were divided into four groups, 8 animals each: Halothane-control, halothane-F, isoflurane-control, isoflurane-F. Animals were anesthetized with 2% isoflurane in oxygen. Two right jugular vein catheters were placed for drug infusion and thermal indicator injection. A 1 Fr. thermal probe was placed in the aortic arch though the left carotid artery to assess thermal dilution wave form. An abdominal aortic catheter for pressure monitoring was placed through the caudal tail artery. The animals were allowed to recover from anesthesia for 24 to 48 hours. On the day of the study baseline hemodynamics including MAP, heart rate, cardiac output, SVR, stroke volume and cardiac work were determined using four 200 ul injections of room temperature saline with a Cardiomax II cardiac output computer. A continuous 5 ug/min/kg infusion of F or vehicle(saline) was started and hemodynamics were reassessed 30 minutes later. Anesthesia was induced and animals were intubated. Arterial blood gases were used to adjust ventilation and maintain normocarbia. Blood temperature was maintained at 38° C ±0.5. Inspired anesthetic was initially maintained at 0.5 MAC in oxygen using an infrared anesthetic monitor. Hemodynamics were assessed 30 minutes later. Anesthetic vapor was then increased to 1, 1.33, 1.66 and 2 MAC in half hour steps with hemodynamic assessment at the end of each anesthetic interval.

Results: Significant differences in hemodynamic parameters were detected by ANOVA(two factor, repeated measures 1 factor). Results for MAP and cardiac output for control levels, and 1 and 2 MAC are illustrated for both anesthetics in Figure 1. F produced a significant drop in MAP (8.5%) during control and isoflurane levels. Both vapors produced a progressive drop in MAP with increasing MAC. However, halothane produced greater reductions in MAP then isoflurane at equivalent MAC. Halothane produced a progressive drop in cardiac output with increasing MAC. Cardiac output was preserved with isoflurane once 1 MAC was achieved. No significant interaction (synergism) between F and anesthetic was detected for any hemodynamic parameter.

Discussion: F infused at 5 ug/min/kg produces a slight but sustained decrease in MAP under isoflurane anesthesia. This dose is five times higher then that required to produce marked increases in renal blood flow in the conscious rat and man. F appears safe to use with anesthetic vapors. This study provides the foundation for future safety and efficacy studies in man.

Figure 1.



1. Mazze RI:Renal physiology and the effects of anesthesia, Anesthesia. Edited by Miller RD, New York, Churchill Livingstone 1986 pp 1223-1246
2. Rigden SP,Barratt TM, Dillon MJ, De Leval M, Stark J: Acute renal failure complicating cardiopulmonary Bypass surgery. Arch Dis Child 57:424-430 1982
3. Ackerman DM, Blumberg AL, McCafferty JP, Shermans SS, Weinstock J, Kaiser C, Berkowitz B: Potential usefulness of renal vasodilators in hypertension and renal disease: SK&f 82526. Fed Proc 42:186-190 1983